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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,425	TAYLOR ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-20 are pending and under consideration in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied, as necessitated by amendment, or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

3. Claims 1-2 and 4-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing or predicting susceptibility to Crohn's disease in an individual comprising detecting the presence or absence in said individual of a 2-2-4 haplotype at the Notch 4, HSP70-HOM and D2S273 loci, wherein the presence of said haplotype is diagnostic of or predictive of susceptibility to Crohn's disease in said individual, does not reasonably provide enablement for a method of diagnosing or predicting susceptibility to any autoimmune disease associated with a 2-2-4 haplotype at the Notch 4, HSP70-HOM and D6S273 loci by detecting the presence of the 2-2-4 haplotype or a method of diagnosis or predicting susceptibility to Crohn's disease by detecting a disease associated haplotype or an allele "associated" with the 2-2-4 haplotype. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to diagnosing or predicting the susceptibility to *any* autoimmune disease associated with the 2-2-4 haplotype in any individual by detecting the presence or absence of a 2-2-4 haplotype at the Notch 4, HSP70-HOM and D6S273 loci. The claims are further drawn to diagnosing or predicting the susceptibility of rheumatoid arthritis, or Type I diabetes, or Crohn's disease, or inflammatory bowel disease in any individual by detecting the presence or absence of a 2-2-4 haplotype at the Notch 4, HSP70-HOM and D6S273 loci. The claims are further drawn to a method of diagnosis or predicting susceptibility to Crohn's disease by detecting a disease associated haplotype "associated" or an allele "associated" with the 2-2-4 haplotype.

The amount of direction or guidance:

The specification teaches that the Notch 4 gene is a member of the Notch gene family which is located near the centromeric end of the MHC class III locus on chromosome 6. The specification teaches that the Notch 4 gene has 7 alleles corresponding to different numbers of tandem repeat of the trinucleotide (CTG) located in exon 1 of the gene. The specification teaches that the "2" allele corresponds to a 325 base pair fragment (pp 6-7). With regard to the HSP70-HOM locus and the D6S273 microsatellite marker, the specification teaches that the HSP70 proteins are indicated in immune response and that the "2" allele corresponds to a T at position 2437 of the HSP70-HOM gene. The specification teaches that the D6S273 locus is a microsatellite polymorphism that is located at nucleotides 34073 to 34114 and that this locus has 7 alleles, the "4" allele corresponding to a 134 bp fragment. The specification teaches how to detect each allele of the 2-2-4 haplotype (see page 30).

The specification does not teach the function of any genes at this locus, nor how the alleles are involved in any of the diseases claimed.

Presence and absence of working examples:

The specification teaches of a study which was composed of 108 patients with CD and 69 ethnically matched control subjects (mainly spouses) who were genotyped (p. 28). The specification teaches that in family studies, an association was found between the Notch4 2 allele and CD (p=.011). The specification teaches that the association increased with detecting of the 2-2 alleles (Notch4 and HSP70-HOM) and the 2-2-4 alleles (Notch4, HSP70-HOM, and D6S273) (p=0.0044 and p=0.00097, respectively, see pages 32-33). In a case control panel, the

specification teaches that the association between the 2-2-4 haplotype and Crohn's disease was stronger than with the Notch4 allele alone (see page 33).

With regard to claims 1-12, the specification provides no working examples of an association between the 2-2-4 haplotype and the broad scope of the diseases encompassed by "autoimmune disease", including autoimmune diseases other than Crohn's disease, which may be associated with the 2-2-4 haplotype at Notch4, HSP70-HOM, and D6S273.

With regard to claims 13-20, the specification provides no working examples of any association between Crohn's disease and a) the presence or absence of a "disease associated haplotype associated with the 2-2-4 haplotype" or b) "a disease associated allele associated with the 2-2-4 haplotype". Additionally, the specification demonstrates at figure 3 that the combination of the HSP70-HOM allele 2 and the D6S273 allele 4 are not associated with Crohn's disease ($p=0.22$). The specification teaches that a "disease associated haplotype associated with the 2-2-4 haplotype" and "a disease associated allele associated with the 2-2-4 haplotype" are haplotypes or alleles that are inherited more often than would be expected according to traditional Mendelian genetics. While the specification provides examples of a few alleles that 'could' be contained within a 'disease associated haplotype" or "a disease associated allele", the specification provides no guidance or examples as to any specific haplotype "associated with" the 2-2-4 haplotype nor does the specification teach how tightly linked the alleles, which are suggested to be associated, are with the 2-2-4 haplotype. It is clear from the teachings of figure 3, for example, that MHC alleles, just by virtue of being MHC alleles, are not predictably associated with Crohn's disease. Additionally, it is clear from the teachings in the specification, that 'disease associated haplotypes and alleles' are population specific. For

example, at page 31, the specification teaches that previous reports found an association between HLA-DRB*0103 and CD, but that such association was observed in non Jews, whereas the teachings in the study taught by the specification, which involved an Ashkenazi Jewish population, did not find an association with CD and that therefore the observations in the specification were not due to linkage disequilibrium between Notch4 and HLA-DRB1. Therefore, while the specification has shown an association between CD and the 2 allele of Notch4, as well as the 2-2-4 haplotype for Notch4, HSP70-HOM, and D6S273, the specification has provided no correlation that an allele in linkage disequilibrium with any of these alleles or haplotype would be predictably associated with Crohn's disease, or any autoimmune disease in general.

The state of the prior art and the predictability or unpredictability of the art:

An association with the claimed haplotype and any autoimmune disease, or any inflammatory bowel disease (IBD), such as ulcerative colitis (UC), based on data only obtained with patients with Crohn's disease (CD) is clearly unpredictable given the state of the art. Rector et al (Genes and Immunity, vol. 2, pp 323-328, October 2001) teach that inflammatory bowel diseases (IBD) in general, as well as CD and UC are complex multifactorial traits involving both environmental and genetic factors (see abstract). Rector teaches that a study of point mutations in codons 52, 54, and 57 of exon 1 of mannan-binding lectin, which plays an important role in non specific immunity, were significantly lower in frequency in UC patients when compared with CD patients. Lesage et al (American Journal of Human Genetics, vol 70, pp 845-857, 2002) teaches that CARD15/NOD2 encodes a protein involved in bacterial recognition by monocytes

and that mutations in CARD15 have been associated with CD. Lesage teaches that an analysis of 3 polymorphisms which were independently associated with susceptibility to CD were not associated to UC (see abstract). Further, Over et al (European Journal of Gastroenterology and Hepatology, vol. 10, pp 827-829, 1998) teaches that a study that tested the frequency of a point mutation in factor V (FV Leiden), which has been identified in various thromboembolic diseases, found that FV Leiden was found to be statistically more frequent in CD patients but not in UC patients (see abstract). Thus, as exemplified by the state of the art regarding polymorphisms in genes or genetic markers and their association with IBD's, an association between specific polymorphisms or mutations and any IBD, such as UC, based on an association with such to CD, is unpredictable. Although polymorphisms in some genes have been linked to both CD and UC, a large number of polymorphisms are also associated to only one disease and not the other, as exemplified by the cited art. Therefore, the art does not provide the skilled artisan with a predictable correlation that polymorphisms, markers, or specific haplotypes linked to CD are also linked to any IBD, such as UC.

An association with the claimed haplotype and either rheumatoid arthritis (RA) and type I diabetes mellitus (IDDM) is also unpredictable as exemplified by the state of the art. For example, Singal et al (Tissue Antigens, vol. 52, pages 353-358; 1998, see page 355) teaches that only the D6S273 132 and 138 bp alleles are associated with RA. Additionally, Kim et al (Tissue Antigens, vol. 54, pages 552-559, 1999) teaches that there was no significant difference between RA and controls in D6S273 alleles (see abstract). Also, Steer et al (Rheumatology, vol. 43, pages 304-307, 2003) demonstrates that two polymorphisms in the CARD15 gene, which were found to contribute to CD disease risk, did not show any significant association to RA (see

abstract and page 306. As such, Steer et al question whether CARD15 is in fact a common autoimmune susceptibility locus. Also of note, Herbon et al (Genomics, vol. 81, pages 510-518; 2003) exemplifies that polymorphisms which are associated with CD, are not necessarily associated with IDDM (see table 1, SNP #4). Thus, as exemplified by the state of the art regarding polymorphisms in genes or susceptibility markers and their association with CD, an association between specific polymorphisms or mutations and any autoimmune disease such as RA or IDDM based on an association with such to CD, is unpredictable. Although polymorphisms in some genes have been linked to both CD and RA or other autoimmune diseases, a large number of polymorphisms or markers are also associated to only one disease and not the other, as exemplified by the cited art. Therefore, the art does not provide the skilled artisan with a predictable correlation that polymorphisms linked to CD are also predictably linked to any autoimmune disease such as RA or IDDM.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

To practice the invention as claimed, the skilled artisan would have to perform a large study of patients with different types of diseases such as UC, RA, and IDDM, and matched controls to determine if the 2-2-4 haplotype or alleles claimed were associated with any autoimmune disease. Such a study would consist of mainly trial and error analysis, the outcome of which is clearly unpredictable as exemplified by the state of the art. Given the lack of

guidance from the specification as to any statistical association between the claimed haplotype and any autoimmune disease other than CD, such as UC, RA, or IDDM, and the unpredictability taught in the art as to an association between polymorphisms or markers associated with both CD and UC, RA, or IDDM for example, the skilled artisan would be required to perform undue experimentation to practice the invention as broadly as it is claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of working examples directed to the broad scope of the claims and the negative teachings in the art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

4. The response traverses the rejection. The response asserts that a strong association between the 2-2-4 haplotype and autoimmune disease is the basis for the claimed methods. The response points to page 7, lines 3-7 and figure 3 for support. This argument has been thoroughly reviewed but was found unpersuasive because the specification only shows an association between the 2-2-4 haplotype and Crohn's disease. No association between this haplotype and any other autoimmune diseases has been shown. Given this lack of guidance from the specification as well as the state of the prior art and the unpredictability taught in the art regarding the lack of a predictable correlation between a specific marker or haplotype and any autoimmune disease based simply on an association between that marker or haplotype and

Crohn's disease, one of skill in the art would be required to perform undue experimentation to practice the invention as broadly as it is claimed. The response further asserts that knowledge of the function of any of the genes of the 2-2-4 haplotype and autoimmune disease would not have been required to diagnose or predict susceptibility as claimed and points to the teachings of Vance et al, at page 323, which states "Allelic association can be explained either by direct biological action of the polymorphism or by linkage disequilibrium with a nearby susceptibility gene". This argument has been thoroughly reviewed but was found unpersuasive. The examiner acknowledges that an allele or haplotype associated with a disease and useful in diagnosis or predicting may have a function relevant to the disease being diagnosed or alternatively may be in linkage disequilibrium with the actual disease causing or susceptibility gene. However, in the instant case, the specification has shown no association between the 2-2-4 and broadly "any" autoimmune disease, such as UC, RA or IDDM, or any of the autoimmune diseases listed in the specification (p. 11-12). As exemplified by the teachings in the art, no predictable correlation can be made with regard to an association between a haplotype or allele and broadly 'any' autoimmune disease based on an association between that haplotype or allele and Crohn's disease. Therefore, also given that neither the specification nor the art provide any guidance as to the function of the genes associated with the claimed haplotype or alleles, or how they would function in any autoimmune disease, one of skill in the art would be required to perform undue experimentation to practice the invention as broadly as it is claimed.

The response asserts (para 2 of page 7 and para 2 of page 8) that claim 1 has been amended to an autoimmune disease "associated with a 2-2-4 haplotype at the Notch4, HSP70-HOM, and D6S273 loci" and therefore does not encompass methods of diagnosing autoimmune

diseases that are not associated with the 2-2-4 haplotype. The response further asserts that only routine methods would be required to confirm association of the 2-2-4 haplotype and an autoimmune disease. This argument has been thoroughly reviewed but was not found persuasive because it is unpredictable as to whether or not any other autoimmune disease or which autoimmune disease is also associated with the 2-2-4 haplotype, as exemplified by the teachings in the art. The response's assertion that the claims do not encompass "inactive" embodiments is not found persuasive because the specification has provided no guidance as to what "active" embodiments are, other than an association between the 2-2-4 haplotype and Crohn's disease. As exemplified by the teachings in the art, the association shown between the 2-2-4 haplotype and Crohn's disease is not commensurate in scope with the claims. The issues raised in the office action are not irrelevant as they specifically address the unpredictability with regard to what 'active' embodiments might be, as exemplified by the teachings in the art. To practice the invention as broadly claimed, a large amount of unpredictable trial and error analysis would be required, which is considered undue.

The response asserts (last para of page 7) that a working example is not required for enablement if one of skill in the art is able to practice the invention without undue experimentation and that with regard to a disease associated haplotype or allele associated with the 2-2-4 haplotype, the use of a surrogate allele or haplotype which is associated with a genetic marker such as the 2-2-4 haplotype having a known association with a disease, is well known in the art. The response further cites portions of the specification which asserts that other haplotypes or alleles which are associated with the 2-2-4 haplotype can be used as a surrogate. This argument as well as the specification have been thoroughly reviewed but were not found

persuasive. As set forth above, one of skill in the art would not be able to practice the claimed invention without undue experimentation. While the specification provides examples of a few alleles that 'could' be contained within a 'disease associated haplotype" or "a disease associated allele", the specification provides no guidance or examples as to any specific haplotype "associated with" the 2-2-4 haplotype nor does the specification teach how tightly linked the alleles, which are suggested to be associated, are with the 2-2-4 haplotype. It is clear from the teachings of figure 3, for example, that MHC alleles, just by virtue of being MHC alleles, are not predictably associated with Crohn's disease. Additionally, it is clear from the teachings in the specification, that 'disease associated haplotypes and alleles' are population specific. For example, at page 31, the specification teaches that previous reports found an association between HLA-DRB*0103 and CD, but that such association was observed in non Jews, whereas the teachings in the study taught by the specification, which involved an Ashkenazi Jewish population, did not find an association with CD and that therefore the observations in the specification were not due to linkage disequilibrium between Notch4 and HLA-DRB1. Therefore, while the specification has shown an association between CD and the 2 allele of Notch4, as well as the 2-2-4 haplotype for Notch4, HSP70-HOM, and D6S273, the specification has provided no correlation that an allele in linkage disequilibrium with any of these alleles or haplotype would be predictably associated with Crohn's disease, or any autoimmune disease in general.

The response asserts (last para of page 8) that guidance is provided in the specification which teaches that the methods of the invention are useful for diagnosing or predicting susceptibility to an autoimmune disease and which lists different types of autoimmune diseases.

This argument has been thoroughly reviewed but was found unpersuasive. The specification only asserts that the methods of the invention are useful for diagnosing or predicting susceptibility to an autoimmune disease, but provides no predictable correlation that the association of the 2-2-4 haplotype and Crohn's disease can be extrapolated to any autoimmune disease. However, given the unpredictability with regards to causes, genetic linkage, and biological properties of the many different types of autoimmune diseases, neither the art nor the specification enable one of skill in the art to extrapolate that because the 2-2-4 haplotype is associated with Crohn's disease in Ashkenizi Jews, that such a haplotype is associated with any autoimmune disease. In light of the unpredictability taught in the art and absent guidance from the specification as to a predictable correlation, the skilled artisan would be required to perform a large amount of unpredictable trial and error analysis, which is considered undue.

The response asserts that a variety of autoimmune diseases were known to share common features, which substantiates that the 2-2-4 haplotype would have been used to diagnose or predict susceptibility to another autoimmune disease as claimed. As support for this assertion, the response provides Becker et al, which teaches that autoimmune diseases share common features and are associated with markers falling into common genetic clusters. This argument as well as the teachings of Becker et al have been thoroughly reviewed but were found unpersuasive to overcome the rejection. While autoimmune diseases share common features, they also possess distinct symptoms, causes, response's to treatment, genetic basis, etc. In the instant case, the specification only exemplifies an association but provides no guidance as to how the 2-2-4 haplotype provides susceptibility to Crohn's disease. Thus, one of skill in the art would be unable to assess how the 2-2-4 haplotype might also be associated to some other

autoimmune disease. Further, the art exemplifies that one cannot extrapolate a predictable association between a haplotype or marker and broadly "any" autoimmune disease based on the fact that an association exists between the haplotype or marker and Crohn's disease. Therefore, absent a showing that the 2-2-4 haplotype is associated with other autoimmune diseases, one of skill in the art would be required to perform trial and error analysis to practice the invention as broadly as it is claimed. The response provides further evidence that the 2-2-4 haplotype can be associated with a variety of autoimmune diseases in addition to Crohn's disease in the reference of Becker which reports that the MHC locus, in which the 2-2-4 haplotype resides, is one of the central genetic factors recognized in autoimmune diseases and in the reference of Vaida et al which indicates that the MHC locus confers 17-20% of the genetic susceptibility to Graves' disease, an autoimmune disease. This argument as well as the cited references have been thoroughly reviewed but were not found persuasive. The reference of Becker does not teach that the 2-2-4 haplotype can be used to diagnose or predict susceptibility to any autoimmune disease. Although Becker states "there may be common genetic factors that predispose to "autoimmunity", Becker does not enable to skilled artisan to practice the invention as broadly as it is claimed because Becker does not teach or suggest that the 2-2-4 haplotype can be used to diagnose or predict susceptibility to any autoimmune disease. Accordingly, the reference of Vaidya does not enable the skilled artisan to practice the invention as broadly as it is claimed because Vaidya does not teach or suggest that the 2-2-4 haplotype can be used to diagnose or predict susceptibility to any autoimmune disease. Further, while the specification provides examples of a few alleles that 'could' be contained within a 'disease associated haplotype" or "a disease associated allele", the specification provides no guidance or examples as to any specific

haplotype "associated with" the 2-2-4 haplotype nor does the specification teach how tightly linked the alleles, which are suggested to be associated, are with the 2-2-4 haplotype. It is clear from the teachings of figure 3, for example, that MHC alleles, just by virtue of being MHC alleles, are not predictably associated with Crohn's disease, let alone any autoimmune disease. Additionally, it is clear from the teachings in the specification, that 'disease associated haplotypes and alleles' are population specific. For example, at page 31, the specification teaches that previous reports found an association between HLA-DRB*0103 and CD, but that such association was observed in non Jews, whereas the teachings in the study taught by the specification, which involved an Ashkenazi Jewish population, did not find an association with CD and that therefore the observations in the specification were not due to linkage disequilibrium between Notch4 and HLA-DRB1.

The response asserts that the specification teaches at page 10, lines 24-33 that the D6S273 locus is associated with type I diabetes and rheumatoid arthritis (RA) further supporting that the 2-2-4 haplotype can be associated with autoimmune diseases such as type I diabetes and RA. This argument, as well as the specification have been thoroughly reviewed but were not found persuasive. As already noted in the previous office action, Singal et al (Tissue Antigens, vol. 52, pages 353-358; 1998, see page 355) teaches that only the D6S273 132 and 138 bp alleles are associated with RA (the 134 bp allele is allele "4"). Therefore, while the D6S273 locus has been associated with IDDM and RA, such is not predictive that a particular allele of that locus, either singly or in a particular haplotype, will be associated with either RA or IDDM, let alone any autoimmune disease. As exemplified by Figure 3 of the specification, the association of the HSP70-HOM "2" and D6S273 "4" alleles in Crohn's disease is not statistically significant in a

haplotype lacking the Notch 4 "2" allele (p=.22). Thus, even if a single allele were found to be associated with a particular disease, it is not predictable to extrapolate an association with that allele and the same disease in any genetic (ie: any haplotype) background.

For these reasons and the reasons made of record above and in the previous office action, the rejection is maintained.

Maintained Rejections

Written Description

5. Claims 13-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13-20 are broadly drawn to a method of diagnosis or predicting susceptibility to Crohn's disease by detecting a disease associated haplotype "associated" or an allele "associated" with the 2-2-4 haplotype. The genus of alleles or haplotypes is very large, and includes uncharacterized haplotypes and alleles from a large portion of the genome.

The specification teaches how to detect each allele of the 2-2-4 haplotype (see page 30). The specification teaches of a study which was composed of 108 patients with CD and 69 ethnically matched control subjects (mainly spouses) who were genotyped (p. 28). The specification teaches that in family studies, an association was found between the Notch4 2 allele and CD (p=.011). The specification teaches that the association increased with detecting of the 2-2 alleles (Notch4 and HSP70-HOM) and the 2-2-4 alleles (Notch4, HSP70-HOM, and

D6S273) (p=0.0044 and p=0.00097, respectively, see pages 32-33). In a case control panel, the specification teaches that the association between the 2-2-4 haplotype and Crohn's disease was stronger than with the Notch4 allele alone (see page 33).

However, the specification provides no description or examples of any association between Crohn's disease and a) the presence or absence of a "disease associated haplotype associated with the 2-2-4 haplotype" or b) "a disease associated allele associated with the 2-2-4 haplotype". Additionally, the specification demonstrates at figure 3 that the combination of the HSP70-HOM allele 2 and the D6S273 allele 4 are not associated with Crohns disease (p=0.22). The specification teaches that a "disease associated haplotype associated with the 2-2-4 haplotype" and "a disease associated allele associated with the 2-2-4 haplotype" are haplotypes or alleles that are inherited more often than would be expected according to traditional Mendelian genetics. While the specification provides examples of a few alleles that 'could' be contained within a 'disease associated haplotype" or "a disease associated allele", the specification provides no guidance or examples as to any specific haplotype "associated with" the 2-2-4 haplotype nor does the specification teach how tightly linked the alleles, which are suggested to be associated, are with the 2-2-4 haplotype. It is clear from the teachings of figure 3, for example, that MHC alleles, just by virtue of being MHC alleles, are not predictably associated with Crohn's disease. Additionally, it is clear from the teachings in the specification, that 'disease associated haplotypes and alleles' are population specific. For example, at page 31, the specification teaches that previous reports found an association between HLA-DRB*0103 and CD, but that such association was observed in non Jews, whereas the teachings in the study taught by the specification, which involved an Ashkenazi Jewish population, did not find an

association with CD and that therefore the observations in the specification were not due to linkage disequilibrium between Notch4 and HLA-DRB1. Therefore, while the specification has shown an association between CD and the 2 allele of Notch4, as well as the 2-2-4 haplotype for Notch4, HSP70-HOM, and D6S273, the specification has not demonstrated that an allele in linkage disequilibrium with any of these alleles or haplotype would be predictably associated with Crohn's disease, or any autoimmune disease in general, nor has the specific described any specific haplotype or allele which is associated with CD and the 2-2-4 haplotype.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). With the exception of the 2-2-4 haplotype, the skilled artisan cannot envision the detailed chemical structure of the encompassed haplotypes or alleles in the genus claimed.

Response to Arguments

6. The response traverses the rejection. The response asserts that the use of a surrogate allele or haplotype which is associated with a genetic marker such as the 2-2-4 haploytpe having a known association with a disease such as Crohn's disease is well known in the art. This rejection has been thoroughly reviewed but was not found persuasive because the art does not teach any surrogate alleles or haplotypes associated with the 2-2-4 haplotype that can be used alternatively to diagnose or predict susceptibility to Crohn's disease. The response asserts that the specification teaches that a disease associated haplotype or disease associated allele

associated with the 2-2-4 haplotype means that the disease associated allele or haplotype and the 2-2-4 haplotype are inherited together more often than would be expected according to traditional Mendelian genetics, and that such can be used as a surrogate for the 2-2-4 haploytpe in diagnosing Crohn's disease. This argument has been thoroughly reviewed but was not found persuasive. The specification provides no description or examples of any association between Crohn's disease and a) the presence or absence of a "disease associated haplotype associated with the 2-2-4 haplotype" or b) "a disease associated allele associated with the 2-2-4 haplotype". Additionally, the specification demonstrates at figure 3 that the combination of the HSP70-HOM allele 2 and the D6S273 allele 4 are not associated with Crohns disease (p=0.22). While the specification provides examples of a few alleles that 'could' be contained within a 'disease associated haplotype" or "a disease associated allele", table 1, figures 2-3, the specification provides no guidance or examples as to any specific haplotype "associated with" the 2-2-4 haplotype nor does the specification teach how tightly linked any of the alleles, which are suggested to be associated, are with the 2-2-4 haplotype. It is clear from the teachings of figure 3, for example, that MHC alleles, just by virtue of being MHC alleles, are not predictably associated with Crohn's disease. As such, the specification has not described a representative portion of the broadly claimed genus of possible associated alleles or haplotype.

Additionally, it is clear from the teachings in the specification, that 'disease associated haplotypes and alleles' are population specific. For example, at page 31, the specification teaches that previous reports found an association between HLA-DRB*0103 and CD, but that such association was observed in non Jews, whereas the teachings in the study taught by the specification, which involved an Ashkenazi Jewish population, did not find an association with

CD and that therefore the observations in the specification were not due to linkage disequilibrium between Notch4 and HLA-DRB1.

Therefore, while the specification has shown an association between CD and the 2 allele of Notch4, as well as the 2-2-4 haplotype for Notch4, HSP70-HOM, and D6S273, the specification has not demonstrated that an allele in linkage disequilibrium with any of these alleles or haplotype would be predictably associated with Crohn's disease, or any autoimmune disease in general, nor has the specific described any specific haplotype or allele which is associated with CD and the 2-2-4 haplotype. For these reasons and the reasons made of record above and in the previous office action, the rejection is maintained.

Double Patenting

7. Claims 1-3 and 5-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,376,176. Although the conflicting claims are not identical, they are not patentably distinct from each other because the broader claims of the instant application (ie genus) are obvious over the more specific (species) claims of the '176 application. For example, the instant claims are drawn to diagnosing or predicting susceptibility to any autoimmune disease by detecting a specific haplotype whereas the claims are more narrowly drawn to detecting Crohn's disease by detecting the same specific haplotype. Additionally, the instant claims are broadly drawn to detection in any individual, whereas the claims of the '176 application are limited to detection in Ashkenazi Jewish individual. The courts have stated that a genus is obvious in view of the teaching of a

species. See Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); and In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

Response to Arguments

8. The response traverses the rejection. The response asks that the rejection be held in abeyance until there is indication of allowable subject matter. It is not the policy of the Office to hold rejections in abeyance. Accordingly the rejection is maintained and made final.

Conclusion

9. No claims are in condition for allowance. Claim 3 is objected to for being dependent on a rejected claim. It would be allowable if rewritten in independent form and upon the filing of a terminal disclaimer.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jehanne Sitton

Jehanne Sitton
Primary Examiner
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6/10/05